Commercial industrial synthesis of Naproxen

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DOI: 10.62579/JAGC0009

Summary

Naproxen, a derivative of α-aryl propionic acid, belongs to the class of Non-Steroidal Anti-Inflammatory Drugs NSAIDs and is commercially available under the name “Aleve”. It is the first Non-Steroidal Anti-Inflammatory NSAID that was isolated in its pure form as the S enantiomer by the Pope -Peachy method. The synthetic processes that have taken place in the industry in recent years are the subject of extensive scientific research and analysis with the aim of improving them to find a more "green", efficient, economical and short process. In this context, a thorough historical review of naproxen is presented, focusing on its development from its commercial application in the early 1970s to its current position. Its synthesis began in 1970 by Syntex with beta-naphthol as a raw material and a production of 500 kg. It was also commercialized by Syntex in 1976. The present industrial synthesis took place in the period 1984-1993, with a yield of 90% using the Pope-Peachy method and a recovery of N-alkylglucamine in each cycle of 98%. A brief reference is made to the chemical structure of the molecule, its pharmacodynamic and pharmacokinetic profile as well as its mechanism of action in order to understand at a later stage the mechanism as well as the catalytic system of the predominant industrial synthesis of naproxen, highlighting the chemical reactions. Through a detailed flow chart, the exact synthesis process is presented, describing each step of the process in technical detail. Finally, statistical data on naproxen's patents and formulation publications are presented, highlighting its global influence and importance in the field of the pharmaceutical industry.

SUBJECT AREA: Industrial Synthesis of Naproxen

KEYWORDS: Naproxen, industrial synthesis, Pope-Peachy, Syntex, historical review, mechanism, catalysts, statistics

LIST OF FIGURES

CATALOG OF IMAGES

LIST OF TABLES

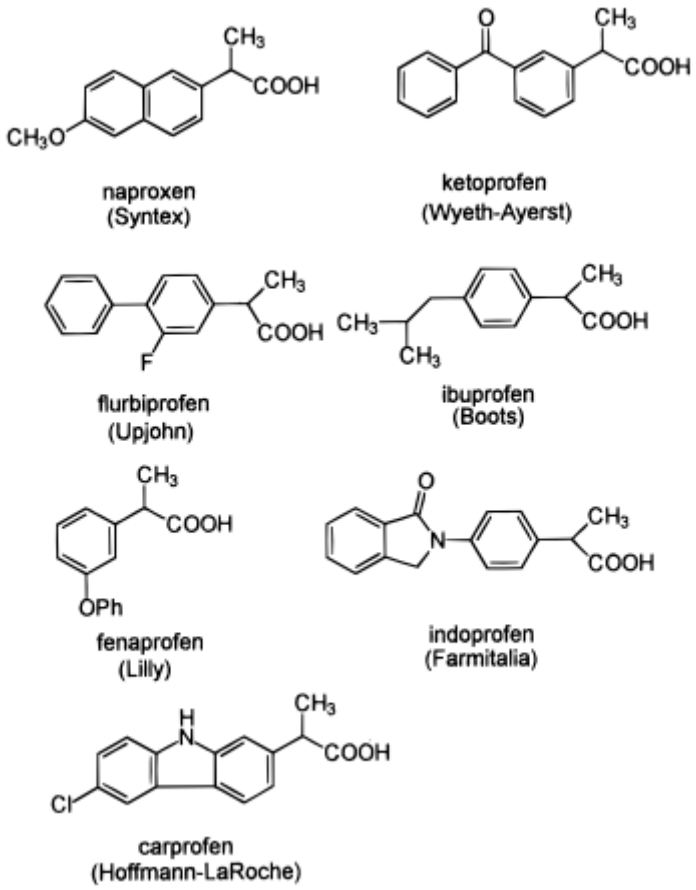
Table 1: World market for optically clear pharmaceuticals in 1991.

Table 2: Total value of exports by country.

Table 3: The amount of Naproxen exported by country.

1. Introduction

The purpose of the paper is to present the predominant production process of naproxen on an industrial scale, but also older methods of its synthesis by the pharmaceutical company, Syntex. Therefore, a brief historical review of naproxen is made from its first large-scale synthesis in 1970 to its second large-scale synthesis in the period 1976-1993.[3] Naproxen is marketed in its pure form, S enantiomer. Figure 1 (below) shows seven of the most well-known Non-Steroidal Anti-Inflammatory drugs, of which only naproxen is found in its pure form.[3]



Picture 1. Non-Steroidal Anti-Inflammatory Drugs.

The choice to study the composition of the particular drug lies in several reasons. Primarily, naproxen is an over-the-counter drug used to treat pain, inflammatory conditions such as rheumatoid arthritis, and fever. It is also available as a generic drug.[1-2] Studies have shown an increased demand for anti-inflammatory drugs, which makes improving the production formulation of naproxen especially important.[4]

At a later stage, continuous efforts to improve the production process of naproxen were identified in the literature which contributed to the improvement of efficiency, production costs but also to the minimization of catalysts or to finding more environmentally friendly catalysts.[3] In 1991, before the patent expired, (S)-naproxen was the fourth best-selling optically pure drug, based on Table 1 (below). Also on the list were the blockers enalapril (first), captopril (second) and lisinopril (sixth), the lipid-lowering drugs lovastatin or mevinolin (third) and simvastatin (seventh), and the calcium antagonist and vasodilator diltiazem (fifth) [3] .It becomes clear, therefore, that huge industrial interests derive from the composition of this particular drug.

pharmaceutical	sales ($ million)
enalapril	1745
captopril	1580
lovastatin	1090
naproxen	971
diltiazem	912
lisinopril	630
simvastatin	400

Table 1. World market for optically clear pharmaceuticals in 1991.[3]

The methodology of this work is mainly focused on gathering and analyzing existing information and data from the literature and other sources. In other words, the creation of an integrated theoretical framework related to the industrial synthesis of naproxen is sought. First, a historical review of Syntex's drug compositions is carried out with an emphasis on the dominant composition, then the chemical structure and characteristics of the molecule, its mechanism of action and its pharmacokinetic profile are examined. Emphasis is placed on the mechanism of the catalytic reaction but also on the characterization of the catalytic system. Then, a flow diagram of the specific chemical process is presented, but also information related to the industrial application of

naproxen; producing countries, plant capacity, and its uses are listed. Finally, various related publications are presented regarding the use of naproxen around the world as well as patents for its composition.

1.1 Historical Review

The first large-scale synthesis of naproxen produced 500kg of material in 1970 by Syntex (Figure 1).[5] Friedel-Crafts acylation of 2-methoxynaphthalene gave 2-acetyl-6-methoxynaphthalene (MAN), which was converted to naphthylacetic acid by the Willgerodt reaction. A-methylation yields the d,l-acid, which can be efficiently resolved using cinchanonidine. This process had several undesirable characteristics. First, the Friedel-Crafts acylation was not regioselective, also producing the 1-isomer, which can be removed by crystallization. Second, aluminum hydroxide waste was produced in significant quantity and buried. Third, there were a number of unwanted reagents in the sequence: nitrobenzene (used in the acylation), ammonium sulfide (used in the Willgerodt reaction), sodium hydride, and methyl iodide.[3]

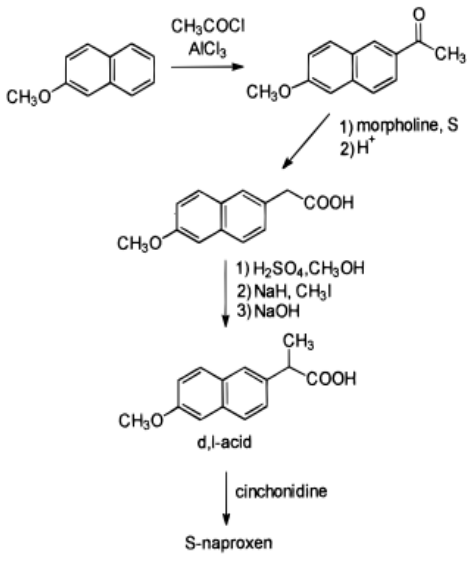


Figure 1. First large-scale synthesis of naproxen (500 kg).[3]

All of these issues were addressed and the first naproxen manufacturing process, implemented in 1972-1975, was dramatically different (Figure 2). Naphthol was brominated in methylene chloride to produce 1,6-dibromonaphthol. Bromine at

position 1 was removed with bisulfite. The resulting 2-bromo-6-hydroxynaphthalene (BHN) was methylated with methyl chloride in water-2-propanol. The yield of 2-bromo-6-methoxynaphthalene (BMN) was 85-90% from β-naphthol. BMN was converted to a Grignard reagent, which was transmetallated with zinc chloride, and then naphthylzinc was coupled with ethyl bromopropionate. Hydrolysis of the ester gave d,l-acid. The yield from BMN to d,l-acid was 50-60%. Again, the cinchonidine assay was effective (95%).[3]

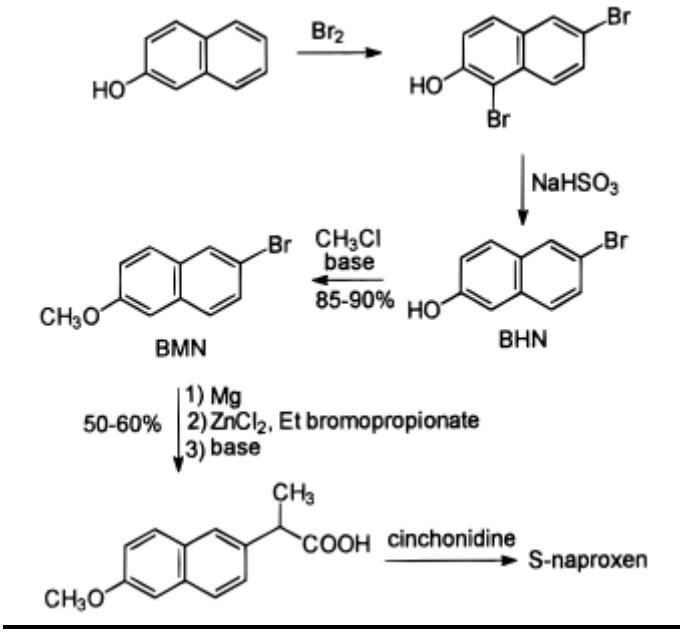


Figure 2. First large-scale production process 1972-1975.[3]

But there were significant problems with this synthetic course as well. First, a stoichiometric amount of zinc chloride was required for the naphthyl-zinc coupling reaction. Large volumes of zinc hydroxide were filtered and landfilled. Second, the yield in the coupling reaction was low. Third, there were two undesired side products in the coupling reaction. The reduction produced 2-methoxynaphthalene, which is volatile and has a "sweet grape" odor - complaints from the local community were common. A radical coupling reaction produced a highly insoluble dinaphthyl "dimer". Unacceptably large quantities of dimer were landfilled with the zinc waste.[3]

The main problems of this first production process were related to the naphthyl-zinc coupling reaction. An alternative coupling to the second manufacturing process, implemented in 1976-1993, eliminated zinc waste and minimized the formation of nerolin and dimers (Figure 3, below). BMN was converted to a Grignard reagent, which was directly coupled to a bromopropionic acid salt. As might be expected, this coupling reaction produced d,l-acid as a component of a complex mixture. In fact, production yields in 1984 were less than 50%. A series of process improvements introduced over the last 10 years have increased efficiency to over 90%! Cinchonidine was replaced by an N-alkylglucamine. Again, the assay was efficient (>95%).[3] The Pope-Peachy method was applied to this industrial synthesis and a 98% recovery of N-alkylglucamine was achieved in each cycle. N-alkylglucamine, usually prepared by reductive amination of D-glucose, is both cheap and readily available.[6]

In 1988, staff at the Syntex Technology Center in Boulder were tasked with evaluating all naproxen synthesis technologies and then developed and implemented the lowest cost naproxen process. At that time, one-third of the total production cost of naproxen was related to the racemic acid, and two-thirds of the production cost (mainly labor) was related to the analysis-racemization. They concluded that reducing the cost of d,l-acid had little benefit. The real savings will come from a more refined resolution or asymmetric technology.[3]

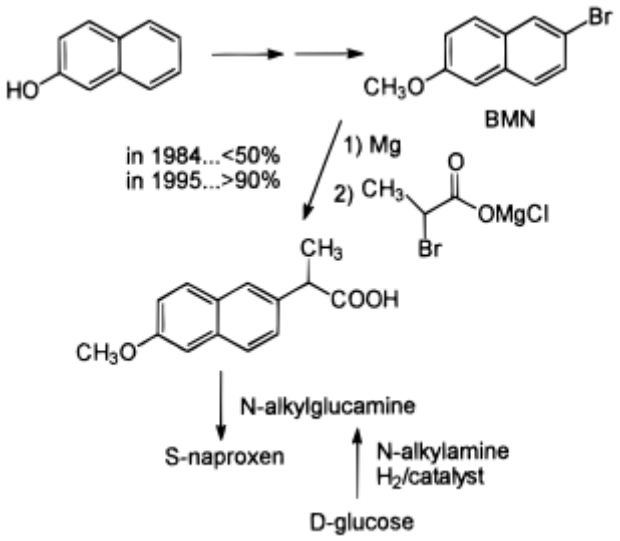


Figure 3. First large-scale production process 1976-1993.[3]

As mentioned above, the pharmaceutical company Syntex dealt with the synthesis of naproxen. It is a company founded in Mexico City in January 1944 by Russell Marker, Emeric Somlo and Federico Lehmann with the aim of manufacturing therapeutic steroid drugs.[7] In 1959, Syntex moved its headquarters to Palo Alto, California and grew into a multinational corporation. After 1959, Syntex was founded in Panama - management, research and marketing were conducted from Palo Alto - steroid production remained in Mexico - and also produced final drugs in factories in Puerto Rico and the Bahamas.[8] Syntex agreed to be acquired by the Roche Group in May 1994.[9]

George Rosenkranz: The "father" of naproxen

George Rosenkranz (1916-2019) was born in Budapest to middle-class Jewish parents. His childhood was marked by an appreciation for the arts, music, theater and education. Although he showed a talent for modern languages, he was particularly drawn to scientific studies, especially chemistry.[11]

In 1933 he left his family home to continue his studies at the Swiss Federal Institute of Technology in Zurich. There, he enrolled in an organic chemistry course taught by future Nobel laureate Lavoslav (Leopold) Ružička. Rosenkranz was deeply influenced by Ružička, who was involved in the synthesis of the male sex hormone testosterone. He sought to continue his studies under the guidance of Ružička. In 1937, Rosenkranz became a doctoral student of Ružička, receiving his degree in 1940. At that time, the Axis countries rose to power. Ružička protected Rosenkranz and his other Jewish colleagues from the Nazis in Zurich, but they decided to leave the city, not wanting to endanger their mentor.

Through connections, Rosenkranz secured a professorship in Ecuador. The plan was to travel to Cuba via Spain and then Ecuador. He made it all the way to Havana, but then the attack on Pearl Harbor caused a world panic and his transfer to Ecuador never took place. Stranded in Cuba, Rosenkranz made the best of the situation and began looking for work. He was hired by the company Vieta-Plasencia Laboratorios, where he developed successful treatments for venereal diseases.[11]

His years at Syntex

In 1945, Rosenkranz received an invitation to interview at a company called Syntex in Mexico City. Syntex was a synthetic hormone research company founded just a year

earlier by chemist Russell Marker and two others.[10] They were trying to make synthetic hormones from diosgenin, a natural plant hormone found in wild Mexican sweet potatoes.[11]

Rosenkranz impressed the interviewers and was immediately offered the position of chief chemist. After a brief return to Havana, Rosenkranz moved to Mexico to begin his tenure at Syntex. He remained with the company throughout his career, occupying the roles of chief executive officer and chairman of the board for a significant part of that period. Retired from Syntex in 1981.[11]

Rosenkranz was able to recruit leading organic chemists, including Carl Djerassi and Alejandro Zaffaroni. Their collaboration proved fruitful. During his career, Rosenkranz and his numerous colleagues developed and refined pioneering advances in the understanding and production techniques of steroid drugs, using native Mexican plant sources as raw materials.[11]

In 1951, Syntex synthesized the first effective oral contraceptive (norethindrone). During his tenure, the company expanded its operations to become the leading supplier of the oral contraceptive pill (commonly referred to as "the pill") and other corticosteroids, permanently changing social structures.

Having succeeded in the field of steroid research, Rosenkranz recognized the need to diversify the company's operations. He and a team of researchers began investigations into the potential of a nonsteroid anti-inflammatory drug for the systemic treatment of rheumatoid arthritis and osteoarthritis. The result of this research was the development of another drug, Naproxen. In the following years, the FDA granted approval for Naproxen for use in the treatment of a wide range of diseases, including osteoarthritis and juvenile arthritis. In 1980, naproxen sodium was introduced to the US market as Anaprox. By 1983, the two drugs had become the best-selling non-steroidal anti-inflammatory drugs in the world. Both products contributed to a significant increase in Syntex's annual sales, which in 1987 reached $1 billion. Alleve, a pain reliever used for conditions such as arthritis, muscle pain, and menstrual cramps, was then launched a few years later, completing Syntex's transformation into a major pharmaceutical company.[12]

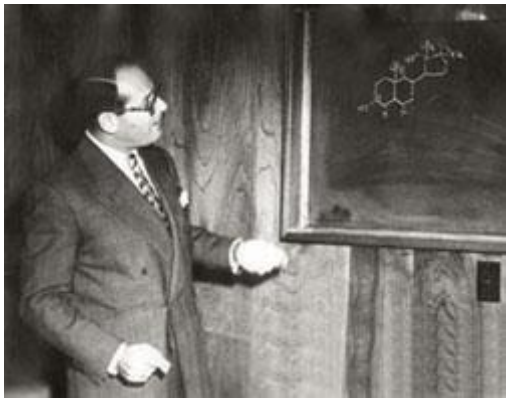
Continued Influence and Recognition

Rosenkranz's legacy continues to be recognized and influential, with his name associated with over 150 patents and over 300 published research articles on steroid hormones. After his retirement, he continued to hold numerous roles in the industry, including as a member of the New York Academy of Sciences and on the boards of Tel Aviv University, the Weizmann Institute of Science, Digital Gene Technologies, and ICT Mexicana. The National Academy of Medicine of Mexico awarded Rosenkranz the distinction of honorary member in recognition of his dedication to scientific work and to the education of his Mexican colleagues at Syntex.[11]

In 2004, Rosenkranz was jointly honored with Alejandro Zaffaroni with the Winthrop-Sears Medal of the Chemists' Club. In 2013, the Biotechnology Innovation Agency and the Chemical Heritage Foundation (now the Institute for the History of Science) presented him with the Biotechnology Heritage Award, recognizing him as a pioneering biopharmaceutical entrepreneur and the mastermind behind Syntex and "the pill".[11]

In addition, Rosenkranz was a highly successful bridge player who authored 15 books on bridge and won.[11]

Picture 2. Dr George Rosenkranz at his home in Mexico.[13]



Picture 3. Dr George Rosenkranz in 1950 draws the structure of a steroid drug.[14]

Picture 4. Dr George Rosenkranz and his research team at Syntex.[15]

1.2 Chemical Structure and Molecule characteristics

Naproxen is an arylalkanoic acid, an aromatic derivative of propionic acid.

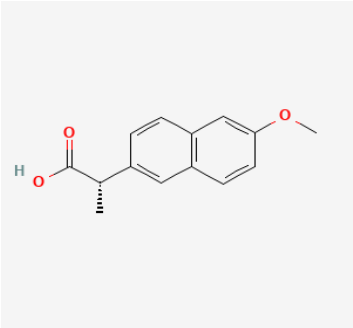
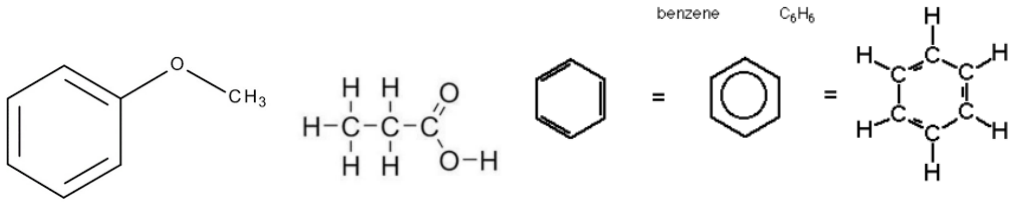


Figure 4. Chemical structure of naproxen molecule.[16]

IUPAC name:(2S)-2-(6-methoxynaphthalen-2-yl) propanoic acid[16]

Trade names:Aleve, Naprosyn[16]



Picture 5. Chemical groups that make up the naproxen molecule.

Listed below are some basic characteristics of the molecule as well as some of its physical and chemical properties:[16]

Molecular weight:230.26 g/mol

XLogP3:3.3

Number of hydrogen bond donors:1

Number of hydrogen bonds accepted:3

Referring to the experimental properties of the molecule, its physical description in the literature is a solid, colorless, crystalline stable powder, with a characteristic odor. Its boiling point is at 402-404°C and melting point at 152-154°C. Naproxen is readily soluble in most organic solvents and very soluble in ethanol, 55 mg/mL.[17]

1.3 Mechanism of Action

Naproxen is a non-narcotic drug with strong anti-inflammatory and antipyretic properties. These properties have been proven in human clinical trials and classic animal studies. Anti-inflammatory effects have also been observed in adrenalectomized animals, indicating that its effects are not determined by the adrenal-pituitary axis.

As with other anti-inflammatory drugs, the exact mechanism of action of naproxen is unknown. Naproxen does not inhibit the CNS and does not induce enzyme production. [17] More specifically, naproxen works by reversibly inhibiting COX-1 and COX-2 enzymes as a non-selective coxib. This results in inhibition of prostaglandin synthesis. Prostaglandins act as signaling molecules in the body, causing inflammation. Thus, by inhibiting COX-1/2, naproxen produces an anti-inflammatory effect.[18]

1.4 Pharmacokinetic profile

Naproxen is freely soluble in water and is rapidly and completely absorbed from the gastrointestinal tract after oral administration.

Rapid and complete absorption results in significant plasma concentrations and analgesic effects within 20 minutes of administration. After each administration, peak plasma concentrations are reached after 1 to 2 hours, depending on the amount of food consumed. Steady-state plasma concentrations develop after 4-5 doses. The biological half-life is approximately 13 hours. At therapeutic levels, more than 99% is bound to plasma proteins.

About 95% of a single dose of naproxen is excreted in the urine as unchanged drug. The rate of excretion has been found to approximately correspond to the rate of disappearance of the drug from the plasma.

2. Catalytic system and mechanism

2.1. Catalytic system characterization

Catalysis is the phenomenon in which certain substances, called catalysts, change the rate of a chemical reaction, usually increasing it, without themselves being consumed and without changing the point of chemical equilibrium predicted by chemical thermodynamics under certain conditions. Catalysis is distinguished into homogeneous, heterogeneous and heterogenised homogeneous catalysis. Regarding the first two categories, it is true that in homogeneous catalysis, the catalyst and reactants are in the same phase, usually in solutions. In heterogeneous catalysis, the catalyst is usually a solid body, while the reactants are in the liquid or gas phase. Because in this case the reaction takes place on the surface of the solid, heterogeneous catalysis is also called surface catalysis. In homogeneous catalysis the catalyst is some well-defined species (molecule, ion, ion complex, enzyme), while in heterogeneous catalysis the catalytic action manifests itself in only certain positions of the catalytic surface, the active sites, whose concentration, and much more the nature , very difficult to determine.[18]

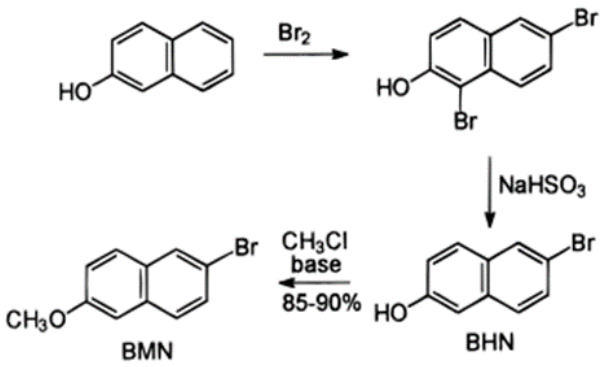


Figure 5: Initial phase of industrial synthesis of naproxen.

According to the picture above, in which the industrial synthesis of naproxen is presented we notice that β-naphthol was brominated to produce 1,6-dibromo-2-naphthol. The labile bromine at the 1-position was then removed with bisulfite and the resulting 6-bromo-2-naphthol (BHN) was methylated with methyl chloride. The yield of 2-bromo-6-methoxynaphthalene (BMN) was 85-90% from β-naphthol.

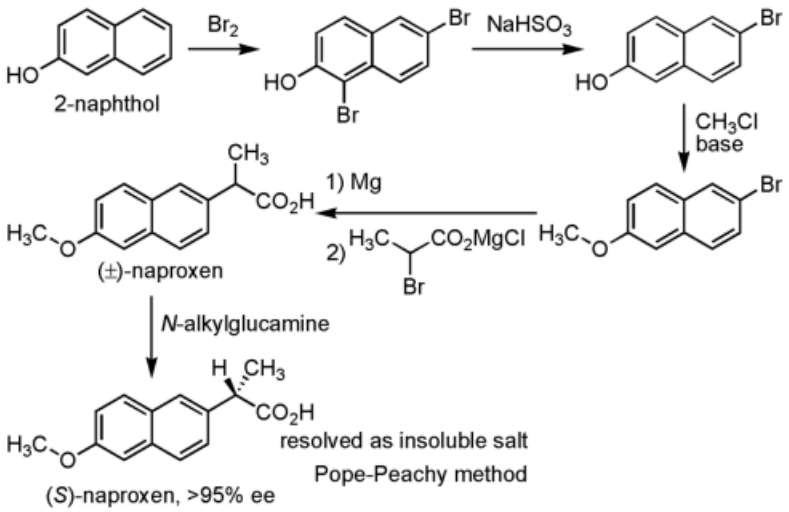


Figure 6: Industrial synthesis of naproxen.

BMN was converted to a Grignard reagent in the presence of Mg (Magnesium), which was directly coupled to a bromopropionic acid salt. As expected, this coupling reaction produced d,l-acid (racemic mixture) as one component of a complex mixture. At the end of the specific industrial synthesis of naproxen is added N-alkylglucamine (Usually prepared by reductive amination of D-glucose and is both a cheap and readily available

reagent), which acts as a solubilizing agent[19] to obtain (S) enantiomer of naproxen with 95% enantiomeric excess.[20] It is generally true that, of the two possible enantiomers, only the (S) enantiomer is used for therapeutic purposes. The majority of known synthetic routes, as happens in this particular case, require the preparation of the racemic mixture, the separation of the (S) enantiomer, racemization of the (R) enantiomer, further separation of the (S) enantiomer, and so on. [21] This process for the separation of the S enantiomer is consistently efficient, with a theoretical yield greater than 95%, and is also much more efficient due to the low cost of the separating agent.[20]

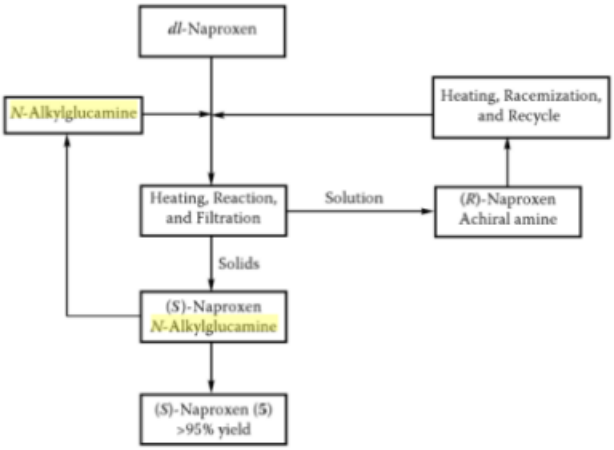


Figure 7. Flow chart of the naproxen assay procedure.

The production of S-naproxen requires continuous improvements of the analytical process in order to achieve dramatic cost reductions. The innovation comes from the in-process racemization and recycling of the by-product, i.e. R-naproxen, and the recovery of the solubilizing agent. In this new and efficient assay procedure, racemic naproxen is reacted with half an equivalent of chiral N-alkylglucamine and another half equivalent of a non-chiral amine. Theoretically, there should be an equilibrium of four different salts in this mixture: the salt of the chiral amine with S-acid, the salt of the achiral amine with S-acid, the salt of the chiral amine with the R-acid, and the salt of the non-chiral amine with the R-acid. However, only the salt of the chiral amine with the S-acid is insoluble in the system and crystallizes. This process drives the equilibrium towards the complete formation of S-naproxen - N-alkylglucamine which

is collected by filtration and upon acidification liberates S-naproxen. The mother liquor, which contains the unwanted acid and the achiral amine, is heated. The amine base catalyzes the racemization of the R-acid—the resulting salt of racemic naproxen and the achiral amine is then recycled through the assay loop in continuous operation. Although each individual run of the assay yields the diastereomer in 45-46%, the overall result of continuous operation produces S-naproxen with 99% ee in greater than 95% yield from the racemic mixture. The recovery of the dissolving agent, N-alkylglucamine, is greater than 98% per cycle. This efficient combination of analysis, racemization, and recycling of both the undesired enantiomer and the analysis agent dramatically increases throughput, reduces cost, and reduces the waste stream, making it ideal for Pope -Peachy analysis. Despite the availability of so many asymmetric and chiral synthetic tank processes, the optimized analytical procedure still proves to be the most cost-effective route for the preparation of S-naproxen. This example demonstrates that classical analytical technology, when combined with appropriate process engineering, can be a superior method for the preparation of chiral industrial chemicals.[22]

Important reagents

During the first step in the synthesis of naproxen, in order to introduce the bromine into the aromatic ring (benzene), the creation of a Lewis acid, iron tribromide $FeBr_3$, is required. Iron tribromide, as can be seen from the mechanism below, is regenerated during the second stage of the bromination of benzene, so it is understood that it is not consumed during the reaction and thus it is also a catalyst for the benzene-bromine reaction. Br_2 first reacts with Fe to form a catalytic amount of $FeBr_3$.

$$3\ Br_2 + 2\ Fe \rightarrow 2\ FeBr_3$$

Picture 6: Reaction of bromine and iron.

In the presence of $FeBr_3$, Br_2 can then brominate the aromatic compound through the formation of a complex that serves as an electrophile, so that nucleophilic attack of the complex from the aromatic ring follows.[23]

2.2. Catalytic reaction mechanism

The mechanism for the industrial synthesis of naproxen is not a known and published subject. Below is a simplified and possible version of it, which is very likely in need of improvement and further analysis.

According to the above total composition of (S) Naproxen it is observed that during the first stage of the mechanism β-Naphthol was brominated to form 1,6-Dibromo-2-naphthol. In order to introduce bromine into the aromatic ring, bromine must first react with iron to form iron tribromide. This is because the bromine atom is sufficiently electrophilic to react with the alkene, but not electrophilic enough to react with the benzene. The presence of iron in the reaction mixture enhances the electrophilic character of the bromine atom. Iron tribromide is a Lewis acid and specifically reacts with Br_2 to form a complex that reacts as if it was Br+. This complex, as shown below, serves as an electrophilic medium that achieves the bromination of the aromatic ring, as shown in the following images.

Regarding the bromination of the benzene ring, in the first step the aromatic ring acts as a nucleophile and attacks the electrophilic medium creating a positively charged intermediate called the Sigma Complex or Arenium Ion, which is stabilized through coordination structures. This stage requires an increase in energy, because it involves a momentary loss of aromatic stabilization. The loss of stabilization occurs because the sigma complex is not aromatic - it does not possess a continuous system of overlapping p orbitals. In the second step of the mechanism, the sigma complex is deprotonated thus restoring aromaticity and regenerating the Lewis acid (FeBr3).[23]

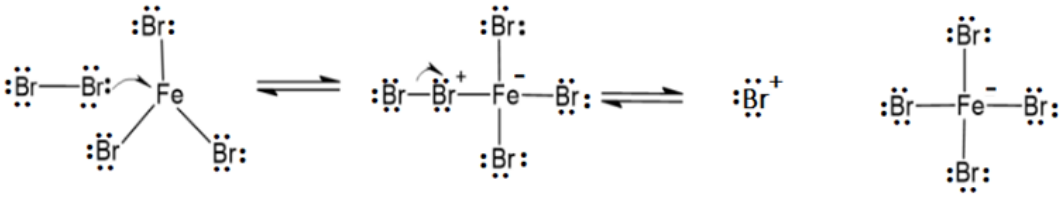


Figure 8. Reaction between bromine and iron tribromide.

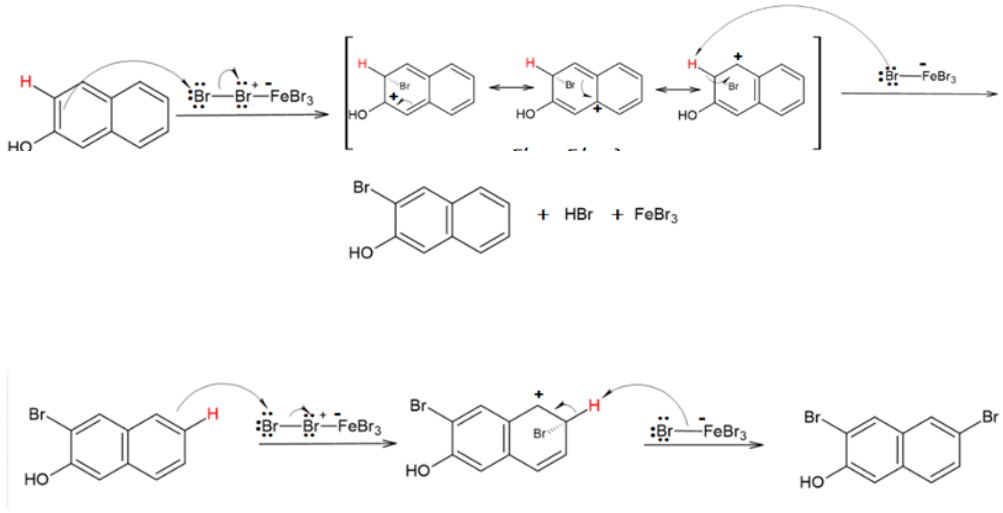


Figure 9. Sequence of steps for synthesis of 6-Bromo-2-naphthol.

The bromine present at the 1-position was then removed with bisulfite ($NaHSO_3$). The reason that the bromine in position 1 is removed is because it is in the benzene ring, in contrast to the bromine in position 6, which is the most stable aromatic ring, while at the same time in benzene there is also the hydroxyl which is a strong activator with the result to increase the stability of the ring so that it is not affected by the removal of the specific bromine atom. The resulting product, 6-Bromo-2-naphthol (BHN), was methylated with methyl chloride and base (indicatively NaOH was used to design the mechanism).

In a next step, Mg is added to form the Grignard reagent. As mentioned above, carbon is more electronegative than magnesium and thus attracts electrons from magnesium by induction. This fact results in the appearance of a negative charge on the carbon atom, with the result that the carbon acts as a nucleophile and is able to attack an electrophile.

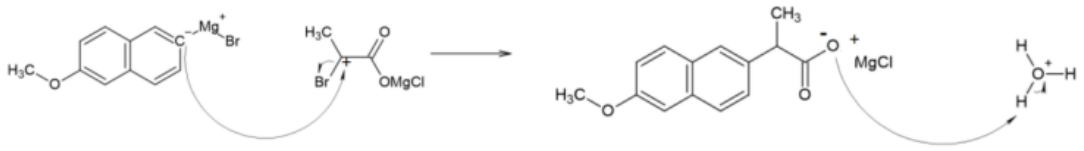


Figure 10. Formation of racemic-acid mixture.

What is then formed is a racemic acid mixture of the two enantiomers of naproxen. This racemic acid reacts with 0.5 equivalents of an achiral amine and 0.5 equivalents of an enantiomerically pure amine (the N-alkylglucamine). The chiral amine salt with (S)-naproxen is precipitated and filtered. The salt of (R)-naproxen with the pure amine remains in the mother liquor and is racemized under heating. The racemic mixture is then subjected to the assay cycle again. In this way the performance in the analysis exceeds 95%.[27]

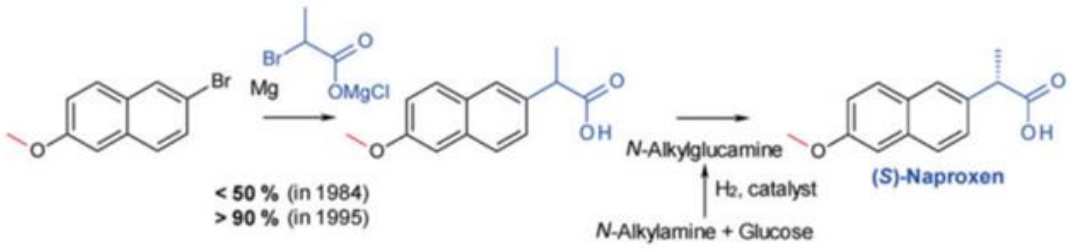


Figure 11. Formation of S-naproxen.

3.Chemical Process Flow Chart

3.1 Importance of Flow Chart

A flowchart (or PFD in this case, process flow diagram) is a visual representation of the flow of a particular system or process that is widely used in many fields, such as

information technology, engineering, business management and industry, to analyze, design and process understanding. It uses specific symbols and arrows to show the sequence of steps or decisions that must be made to complete a process. The basic types of symbols used in a flowchart include terminals, processes, decisions, connections, and inputs/outputs. Each symbol has a specific meaning and is used to represent a specific step. It is therefore an important tool in process analysis, as it presents the various steps of a process in sequential order. It can be adapted to cover a wide range of purposes and describe various processes, such as production, administration, services or project plans. In the case of Industrial synthesis, the flowchart is used to:

1. Analyze the production process of a particular product based on the flow of reactants in the appropriate reactors.

2. Visualize the sequence of actions required for the production of the selected product, as it provides a complete picture of the production or operation processes of an industry, facilitating the understanding of the process, i.e. the workflow process and the connection of the various stages and extend the identification of possible points of improvement.

3. Predict process efficiency, detect potential problems and improve production performance.

4. Be used as a training tool to train new employees or retrain staff in different processes.[28]

3.2 Flow Chart of Industrial Catalyzed Synthesis of S-Naproxen

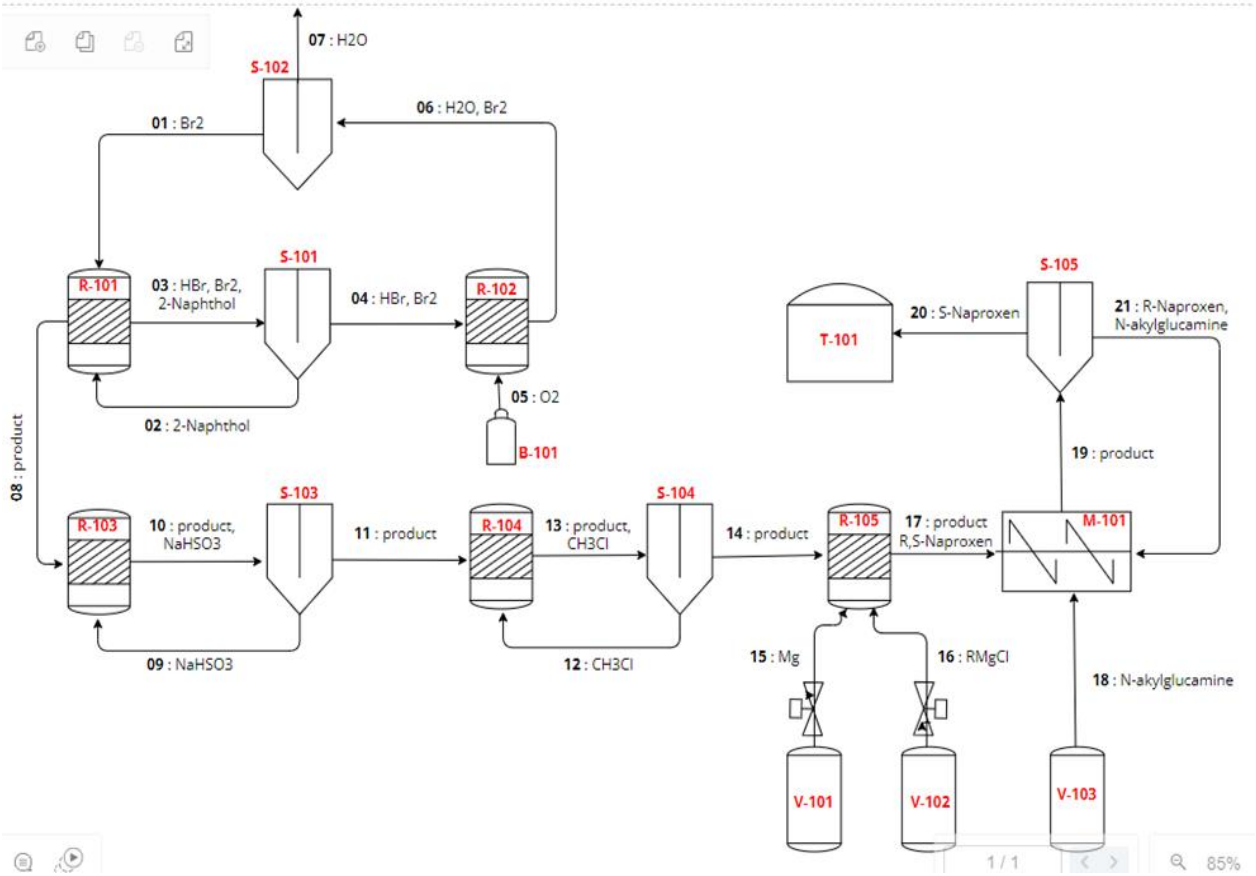


Figure 12.S-Naproxen Flow Chart.

The industrial production of S-Naproxen as shown in the diagram above is a process of several steps. In terms of equipment, a series of reactors and separators are used which serve respectively to carry out reactions and to recycle the reactants back to the reactors in order to achieve the maximum possible efficiency with the least consumption of raw materials. Suitable containers and gas bottles have been chosen to store the necessary reagents, while electronic valves are adapted to reactant containers, specifically in the step of adding the Grignard reagent, as the reaction must take place in the same reactor but with a controlled flow of reactants. In the final stage, the device has a Mixer that creates the appropriate stirring conditions required to form the desired product and store it in the final tank.

Regarding the raw materials used, the Grignard reagent has the role of reactant while the Br2 introduced during the first stage. In addition, it is important to mention that in the given composition the N-alkylglucamine compound is used as a solvent in the last

step. This is a relatively new technique known as the Pope - Peachey method, where the previously mentioned solvent, which in its preparation uses reduction by hydrogen, manages to separate the racemic mixture of naproxen formed when the Grignard reagent is added. S-Naproxen is about 28 times more effective than its R-enantiomer, which justifies the desire to separate them. S-Naproxen can be obtained by enantioselective synthesis but this is expensive and time consuming. The racemic mixture can be readily prepared using a well-developed and optimized method (see PFD Diagram) on a large scale. Currently, most of the enantiopure drug is prepared from the analysis of R,S-Naproxen. R,S-Naproxen is a racemic mixture. It consists of the two enantiomers, R-Naproxen and S-Naproxen, which have identical physical properties and cannot be separated. Therefore, the recovery process (Resolution) is performed by the Pope -Peachey method, an analytical technique based on the formation of diastereomeric salts. The original separation method developed by Pope-Peachey involved adding the separation solvent and a non-chiral auxiliary (achiral base in this case) to the racemic mixture, each in half-equivalent amounts. The separating solvent formed a compound, typically a salt, preferably with one of the enantiomers and caused precipitation of (S-Naproxen). The achiral base increased the solubility of the unreacted mixture of enantiomers and thus the precipitated compound could be removed by simple filtration. However, the now modified method omits the achiral base, relying on the solubility difference between the solvent separation-enantiomer compound and the unreacted enantiomers. In this case N-alkylglucamine is used, a selected base (separation solvent) ideal for the enantiomeric acids (R-Naproxen & S-Naproxen) which will react giving as products of this neutralization reaction (acid + base reaction), salts. The salts formed are no longer enantiomers but diastereoisomers, so they have different physical properties and can reasonably be separated. With this method, not only can the two enantiomers be separated by simultaneously recycling the solvent in each step, but the "unwanted" enantiomer (R) is converted to the desired (S), instead of being discarded, effectively doubling the yield of the product (>95% ee).

4. Industrial application

4.1 Production countries, unit capacity

Naproxen is produced in large quantities and marketed by many pharmaceutical companies worldwide. The largest producers are in India, China and the United States. The production capacity of these companies ranges from a few tons per year to several thousand tons per year, depending on the size of the company and the demand for the product. Some of the major naproxen producers and their production capacities are as follows:

- Bayer (Germany): 2,500 metric tons per year
- Pfizer (USA): 2,000 metric tons per year
- Yung Shin (Taiwan): 600 metric tons per year
- Almirall (Spain): 250 metric tons per year
- Mylan (USA): 200 metric tons per year

It is important to note that some information may not be available to the public as it may be proprietary information held by the companies that produce and use the particular compound. [29]

According to Volza's global export data, Naproxen export shipments from the world are 21.7 thousand, exports from 1,335 Global Exporters to 2,385 Buyers. Globally most of Naproxen is exported to the United States, India and Bangladesh. The top 3 exporters of Naproxen are India with 14,869 shipments, followed by Mexico with 1,716 and the United States in 3rd place with 1,275 shipments.

According to Volza's global import data, Naproxen import shipments in the world totaled 21.7 thousand, imported by 2,385 Global Importers from 1,335 Suppliers. Globally most Naproxen is imported from India, Mexico and the United States. The top 3 importers of Naproxen are the United States with 6,768 shipments followed by India with 2,682 and Bangladesh in 3rd place with 979 shipments. [30]

According to data obtained from the US Department of Customs, $194,571,772 worth of Naproxen has been exported to 74 countries. The average export price for naproxen was $0.46. The United States was the largest importer of naproxen accounting for

60.5% of total naproxen exports. The United Kingdom was the second largest importer of naproxen accounting for 7.3% of total naproxen exports. The month of June 2016 represented the highest number of export shipments. There are 192 naproxen exporters and 69 naproxen importers.[31]

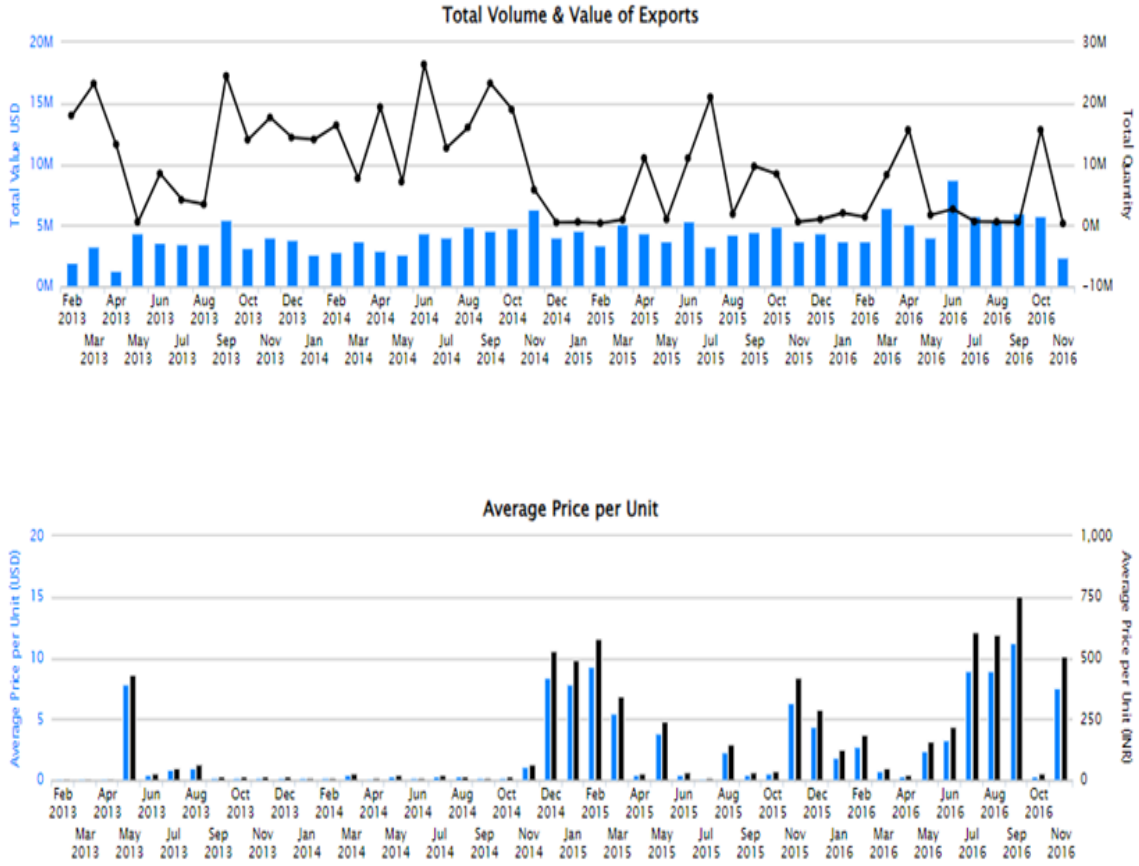


Figure 13. Naproxen export volume per month as well as its corresponding value.

United States	60.5%
United Kingdom	7.3%
Canada	6.2%
Spain	4.9%
Bangladesh	3.1%
Mexico	2.8%
Russia	2.6%
Germany	1.9%
Malta	1.5%
Turkey	1.4%
Iran	1.3%
Philippines	1.1%
Australia	1.1%
New Zealand	0.8%
Ireland	0.8%
Argentina	0.7%
Pakistan	0.7%
Finland	0.7%
Poland	0.6%

Table 2: Total value of exports by country.

United States	86.0%
United Kingdom	11.7%
Malta	1.0%
Canada	0.3%
Honduras	0.1%
Gautemala	0.0%
Australia	0.0%
El Salvador	0.0%
Peru	0.0%
Spain	0.0%
New Zealand	0.0%
Bangladesh	0.0%
South Africa	0.0%
Mexico	0.0%
Philippines	0.0%
Russia	0.0%
Afghanistan	0.0%
Germany	0.0%
Iran	0.0%

Table 3: The quantity of Naproxen exported by country.

4.2. Forms and uses

Naproxen is mainly used as an analgesic and anti-inflammatory drug. It belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDS). NSAIDs are drugs that reduce inflammation, pain and fever with Naproxen being among the three most common along with Aspirin and Ibuprofen. NSAIDs are available in the following four forms: [32]

1)Tablets or capsules

2)Liquid

3)Gels and creams

4)Assumptions

Naproxen in its pure form is mainly found as tablets or capsules [33] and as a liquid. [34] In addition, it is also available in the form of suppositories,[35] while in gel form it is mainly contained as an ingredient (eg Naprosyl gel) and not as pure Naproxen gel.[36]

Naproxen is a structural element in the composition of pharmaceutical products, agrochemicals and perfumes. It is also used in the manufacture of polypropylene fibers and other materials, as well as in the production of polymers and plastics. However, its most widespread use is found in the Pharmaceutical Industry, since as mentioned above it is classified among the widespread NSAIDs. Health care providers use NSAIDs to treat a wide range of symptoms, from headaches and toothache to arthritis and muscle stiffness. Naproxen is primarily used to treat: [37]

- Muscle pains
- Arthritis
- Tendonitis
- Back pain
- Folliculitis
- Toothache
- Menstrual cramps

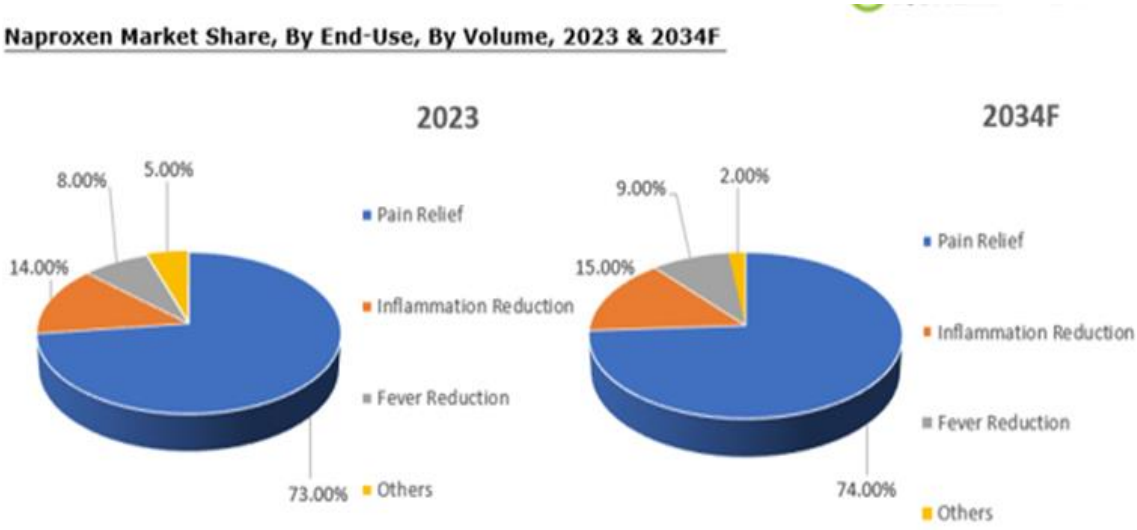


Figure 14. The value of naproxen in the market, by use and by volume by decades

In conclusion, Naproxen has a wide range of uses in both the medical and industrial fields, with the former being the most widespread, making it a versatile and important chemical compound.

5. Statistical analysis of publications and patents of naproxen

The composition of naproxen has been the subject of numerous scientific publications around the world. After a search of the "ScienceDirect" database, a significant increase in the number of scientific articles related to the synthesis of naproxen in the science of pharmacology was found during the last decade. [42] In 2010, approximately 500 publications were recorded on this topic, but this number has tripled to date. Now that is, the publications that have as their main topic the synthesis of naproxen, have exceeded 1,500. [38] Geographically, the United States holds 30% of all publications, China 20%, India 15% while Europe as a whole holds 25% of publications. The remaining 10% is scattered mainly in the African Continent.[38].

Regarding the distribution of publications, there are significant changes over the years, with China showing the fastest growth rate, from 50 publications in 2010 to 300 publications in 2020. [41,42] Furthermore, 60% of publications are research articles. , while the remaining 40% consists of reviews, discussions and comments. These

publications cover a wide range of topics, such as synthesis methodologies (40% of publications), elucidation of naproxen mechanisms of action (25%), naproxen activity (20%), and applications of naproxen in pharmacological research and synthesis new medicinal substances (15%). [41,42]

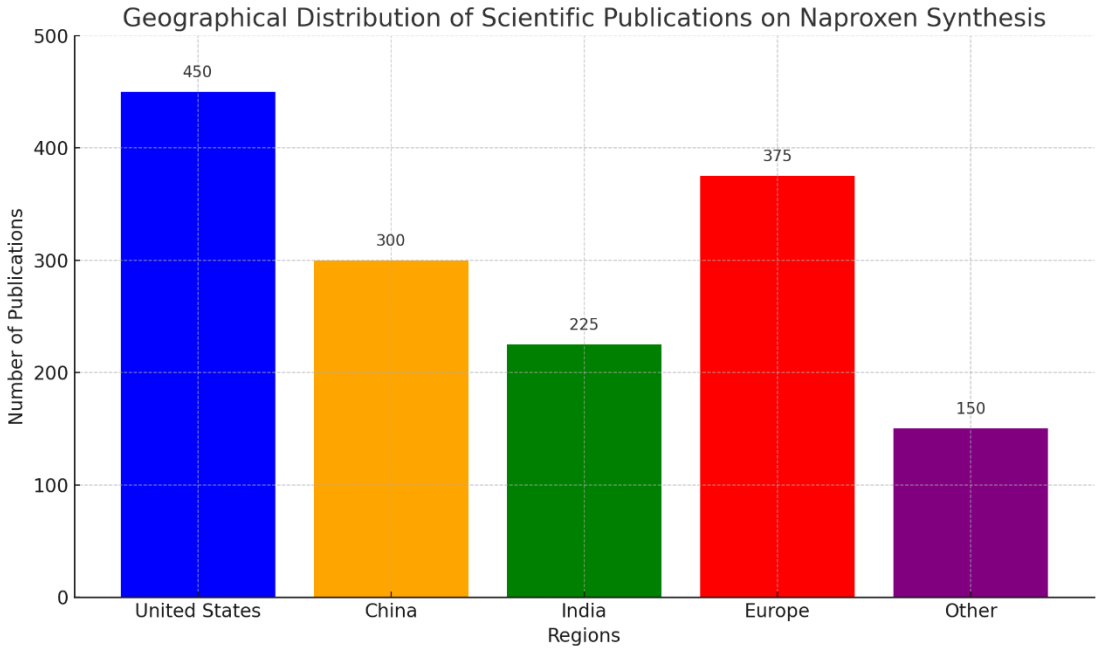


Figure 15. Naproxen publication numbers worldwide.

The industrial formulation of naproxen has also led to an increase in patents worldwide. Patent databases such as those of the United States Patent and Trademark Office (USPTO) and the European Patent Office (EPO) reveal a remarkable escalation of patent applications related to methods of naproxen synthesis. In particular, from 2019 to 2024, the number of patents on naproxen saw an exponential increase in which 500 patents exceeded 2,000 patents worldwide. [39,40,43]

Novartis, Pfizer and GlaxoSmithKline collectively hold approximately 40% of the total patents granted, indicative of their continued research and development. These patents include a wide range of innovations, such as new synthesis techniques (representing 55% of the patents), ways to create more active and pure naproxen (25%), new ways of drug delivery for increased bioavailability (20%). [40, 43]

6. Conclusions

At present study of the pharmaceutical preparation "S-Naproxen" highlighted its important pharmacological action as well as the ways in which this therapeutic substance is prepared. The historical course from the discovery of naproxen to its widespread use today was examined. The production process of the medicinal substance and the importance of active catalytic centers in this process were fully analyzed. This understanding of the mechanism consequently contributes to the design of new effective drugs against each disease.

Furthermore, the analysis of statistical data on publications and patents reveals the wide range of research conducted around naproxen, as well as the competition that characterizes the pharmaceutical industry market. It is anticipated that even more publications and patents will be issued in the future to further optimize this drug. In this way, the practice of medical science will be effectively applied, with the aim of treating patients and improving their quality of life.

However, there is an urgent need to carry out more literature reviews on the medicinal substance of naproxen. The side effects of the drug and all its effects on the human body can be thoroughly studied, in order to highlight the correct health and safety rules for this drug. It is also good to investigate in detail how it affects the tricarboxylic acid cycle of cells, the metabolic pathway of glycolysis, platelet activating factor and cholesterol synthesis and storage in organisms. Based on these investigations, useful conclusions will be drawn, which will help people to understand the correct way to administer the medicine, based on their individual physical characteristics. Various unwanted reactions of the drug in the body will therefore be avoided and the health of consumers will be protected to the highest degree.

7. Bibliography

All websites accessed in April-May 2024

1. Drugs.com. (n.d.). Naproxen Monograph for professionals. https://www.drugs.com/monograph/naproxen.html
2. Ong, C. K. S., Lirk, P., Tan, C., & Seymour, R. A. (2007). An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clinical Medicine & Research, 5*(1), 19–34. https://doi.org/10.3121/cmr.2007.698
3. Harrington, A. P. J., & Lodewijk, E. (1997). Twenty years of Naproxen technology. *Organic Process Research & Development, 1*(1), 72–76. https://doi.org/10.1021/op960009e
4. Harrison, I. T., Lewis, B. M., Nelson, P. A., Rooks, W. H., Roszkowski, A. P., Tomolonis, A. J., & Fried, J. H. (1970). Nonsteroidal anti-inflammatory agents. I. 6-Substituted 2-naphthylacetic acids. *Journal of Medicinal Chemistry, 13*(2), 203–205. https://doi.org/10.1021/jm00296a008
5. Central Business Informatics Journal. (2012). Research Paper 5. https://cbijournal.com/paper-archive/jan-feb-2012-vol-1/Research-Paper-5.pdf
6. Gereffi, G. (1983). *The pharmaceutical industry and dependency in the third world* (2017 reprint ed.). Princeton University Press. ISBN 9781400886227.
7. Freudenheim, M. (1994, May 3). Roche set to acquire Syntex. *The New York Times*.
8. Chemical Heritage Foundation. (2013). George Rosenkranz receives Biotechnology Heritage Award. https://web.archive.org/web/20160712193832/http://www.chemheritage.org/about/news-and-press/press-releases/2013-04-21-george-rosenkranz-biotechnology-heritage-award.aspx
9. Pan American Health Organization. (n.d.). The contribution of PAHO/WHO in the development of the pharmaceutical industry. https://www3.paho.org/English/DD/PIN/Number13_article4_5.htm
10. Science History Institute. (n.d.). George Rosenkranz: Scientific Biographies. https://www.sciencehistory.org/education/scientific-biographies/george-rosenkranz/
11. Pan American Health Organization. (n.d.). The pharmaceutical industry in Latin America. https://www3.paho.org/English/DD/PIN/Number13_article4_1.htm
12. Pan American Health Organization. (n.d.). The pharmaceutical industry: A complex reality. https://www3.paho.org/English/DD/PIN/Number13_article4_2.htm
13. Pan American Health Organization. (n.d.). Pharmaceutical production in the region. https://www3.paho.org/English/DD/PIN/Number13_article4_3.htm
14. National Center for Biotechnology Information. (n.d.). PubChem: Naproxen. https://pubchem.ncbi.nlm.nih.gov/compound/Naproxen#section=2D-Structure
15. Cayman Chemical Company. (n.d.). Naproxen (CAS 22204-53-1) - Product insert. https://cdn.caymanchem.com/cdn/insert/70290.pdf
16. Hawkey, C. J., Langman, M. J. S., Harper, S. E., Thompson, C., Lanas, A., & Logan, R. F. A. (2000). Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. *Journal of Clinical Pharmacology, 40*(10), 1109–1120. https://doi.org/10.1177/009127000004001005
17. Galinos. (n.d.). Naproxen: Pharmacology. https://www.galinos.gr/web/drugs/main/substances/naproxen/pharmacology

18. Hagen, J. (2015). *Industrial Catalysis: A Practical Approach*. https://doi.org/10.1002/9783527684625
19. Acetti, D., Brenna, E., Fronza, G., & Fuganti, C. (2008). Monitoring the synthetic procedures of commercial drugs by 2H NMR spectroscopy: The case of ibuprofen and naproxen. *Talanta, 76*(3), 651–655. https://doi.org/10.1016/j.talanta.2008.04.009
20. Harrington, A. P. J., & Lodewijk, E. (1997). Twenty years of Naproxen technology. *Organic Process Research and Development, 1*(1), 72-76. https://doi.org/10.1021/op960009e
21. European Patent Office. (1985). Process for preparing naproxen. *EP 0163338 A1*. https://patentimages.storage.googleapis.com/32/89/4c/b5ba37c57d44e0/EP0163338A1.pdf
22. Ager, D. (2005). *Handbook of Chiral Chemicals*. CRC Press by Taylor & Francis Group.
23. Klein, D. (2015). *Organic Chemistry* (2nd American ed., 1st Greek ed.). Johns Hopkins University.
24. Drapeau, M. P., Lafantaisie, M., & Ollevier, T. (2013). Iron(III) Bromide. *Encyclopedia of Reagents for Organic Synthesis*. https://doi.org/10.1002/047084289x.rn01568
25. Deng, Q., Shen, R., Ding, R., & Zhang, L. (2016). Bromination of aromatic compounds using bromine in a microreactor. *Chemical Engineering & Technology, 39*(8), 1445–1450. https://doi.org/10.1002/ceat.201400723
26. Wang, W., Lu, K., Qin, Y., Yao, W., Yuan, D., Pullarkat, S. A., Xu, L., & Ma, M. (2020). Grignard reagents-catalyzed hydroboration of aldehydes and ketones. *Tetrahedron, 76*(18). https://doi.org/10.1016/j.tet.2020.131145
27. Schaefer, B. (2015). *Natural Products in the Chemical Industry*. Springer.

28. Kemper, B., De Mast, J., & Mandjes, M. (2009). Modeling process flow using diagrams. *Quality and Reliability Engineering International, 26*(4), 341–349. https://doi.org/10.1002/qre.1061
29. World Health Organization. (2023). WHO Model List of Essential Medicines - 23rd list, 2023. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02
30. Volza. (2023). Naproxen exports from world - Export data with price, buyer, supplier, HSN code. https://www.volza.com/p/naproxen/export/
31. Zauba. (n.d.). Export data and price of Naproxen. https://www.zauba.com/export-naproxen-hs-code.html
32. Cleveland Clinic. (n.d.). NSAIDs (Nonsteroidal Anti-Inflammatory Drugs). https://my.clevelandclinic.org/health/treatments/11086-non-steroidal-anti-inflammatory-medicines-nsaids
33. Deep Heat Australia. (n.d.). Pain relief naproxen liquid capsules. https://www.deepheat.com.au/products/pain-relief-naproxen-liquid-capsules
34. Electronic Medicines Compendium. (n.d.). Naproxen 500mg tablets - Summary of product characteristics (SmPC). https://www.medicines.org.uk/emc/product/14308/smpc#gref
35. Familiprix. (n.d.). Pms Naproxen 500mg suppository – Medication guide. https://www.familiprix.com/en/medications/pms-naproxen-500mg-suppository-02017237
36. Minerva Pharmaceutical. (n.d.). Naprosyn gel. https://www.minervapharmaceutical.gr/product/naprosyn-gel/
37. Cleveland Clinic. (n.d.). NSAIDs (Nonsteroidal Anti-Inflammatory Drugs). https://my.clevelandclinic.org/health/treatments/11086-non-steroidal-anti-inflammatory-medicines-nsaids

*Process Flow Diagram Software. (n.d.). Visual Paradigm. https://www.visual-paradigm.com/features/flowchart-software/

38. Brutzkus, J. C., Shahrokhi, M., & Varacallo, M. (2023). Naproxen. In *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing. PMID: 30247840.
39. European Patent Office. (n.d.). Search results for naproxen synthesis. https://www.epo.org/en/results?search_type=website&q=naproxen%2Bsynthesis&filters=%5B%5D&sortField=&sortDirection=&tab=all_results
40. Google Patents. (n.d.). Search results for naproxen synthesis. https://patents.google.com/?q=%28naproxen%2Bsynthesis%29
41. Ha, M. W., & Paek, S. M. (2021). Recent advances in the synthesis of ibuprofen and naproxen. *Molecules, 26*(16), 4792. https://doi.org/10.3390/molecules26164792
42. ScienceDirect. (n.d.). Search results for naproxen synthesis. https://www.sciencedirect.com/search?qs=naproxen+synthesis
43. U.S. Patent and Trademark Office. (n.d.). Search results for naproxen synthesis. https://www-search.uspto.gov/WWW-search.html